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Original Investigation

Americans' Use of Dietary Supplements That Are Potentially Harmful in CKD

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Background: The prevalence in the United States of dietary supplement use that may be harmful to those with chronic kidney disease (CKD) is unknown. We sought to characterize potentially harmful supplement use by individual CKD status.

Study Design: Cross-sectional national survey (National Health and Nutrition Examination Survey, 1999-2008).

Setting & Participants: Community-based survey of 21,169 nonpregnant noninstitutionalized US civilian adults (aged ≥20 years).

Predictor: CKD status (no CKD, at risk of CKD [presence of diabetes, hypertension, and/or cardiovascular disease], stages 1/2 [albuminuria only (albumin-creatinine ratio ≥30 mg/g)], or stages 3/4 [estimated glomerular filtration rate of 15-59 mL/min/1.73 m^2]).

Outcome: Self-reported use of dietary supplements containing any of 37 herbs the National Kidney Foundation identified as potentially harmful in the setting of CKD.

Measurements: Albuminuria and estimated glomerular filtration rate assessed from urine and blood samples; demographics and comorbid conditions assessed by standardized questionnaire.

Results: An estimated 8.0% of US adults reported potentially harmful supplement use within the last 30 days. A lower crude estimated prevalence of potentially harmful supplement use was associated with higher CKD severity (no CKD, 8.5%; at risk, 8.0%; stages 1/2, 6.1%; and stages 3/4, 6.2%; $P < 0.001$). However, after adjustment for confounders, those with or at risk of CKD were as likely to use a potentially harmful supplement as those without CKD: at-risk OR, 0.93 (95% CI, 0.79-1.09); stages 1/2 OR, 0.83 (95% CI, 0.64-1.08); and stages 3/4 OR, 0.87 (95% CI, 0.63-1.18); all versus no CKD.

Limitations: Herb content was not available and the list of potentially harmful supplements examined is unlikely to be exhaustive.

Conclusions: The use of dietary supplements potentially harmful to people with CKD is common regardless of CKD status. Health care providers should discuss the use and potential risks of supplements with patients with and at risk of CKD.

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INDEX WORDS: Dietary supplements; chronic kidney disease; risk factor.

Chronic kidney disease (CKD) in the United States is common, affecting an estimated 14% of the general adult population who are 20 years or older.[1] Currently, more than 600,000 Americans have progressed to chronic kidney failure requiring renal replacement therapy, a condition that is associated with excess morbidity and mortality.[2] Therefore, it is critically important to identify possible risks for and measures to decrease CKD progression.

Avoidance of substances that may be harmful to the kidney is one important method of reducing CKD progression. Although many herbs commonly found in dietary supplements can cause acute kidney injury and other forms of kidney injury,[3] they are not subject to rigorous governmental standards for content or safety for the general population[4] or for individuals with CKD, for whom the consequences could be particularly deleterious. Because about half of US

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adults report using dietary supplements,[5,6] these products may be an important source of adverse renal effects that are under-recognized by both patients and providers.

To our knowledge, only a few small studies[7-9] have described the use of dietary supplements in patients with CKD, or more specifically, end-stage renal disease, and none have focused on supplements that may be harmful in the setting of kidney disease. In a nationally representative sample, we sought to characterize the extent of dietary supplement use that may have harmful consequences for persons with or at risk of CKD.

METHODS

Study Population

The study population was drawn from the National Health and Nutrition Examination Survey (NHANES).[10] NHANES is a well-established representative survey of noninstitutionalized civilian residents in the United States conducted by the National Center for Health Statistics of the US Centers for Disease Control and Prevention. It consists of a standardized in-home interview followed by physical examination and blood and urine collection at a mobile examination center. All participants provide written informed consent. The protocol was approved by the National Center for Health Statistics Research Ethics Review Board. We included 21,169 nonpregnant adult participants from NHANES 1999-2008 who met our study criteria. From a denominator of 24,693 adults 20 years and older, we excluded 9 with missing dietary supplement use data, an additional 2,262 with missing kidney function data, and finally 1,253 more with estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2. We excluded those with very low eGFR because our goal was to focus on individuals who would benefit most from identifying behaviors that may predispose to nephrotoxicity or CKD progression. After these exclusions, there were no pregnant participants remaining.

Measurements

Serum creatinine was measured by the modified kinetic method of Jaffé using different analyzers in different survey years. Creatinine levels were calibrated as specified in NHANES documentation.[11,12] Random spot urine samples were obtained, urine albumin was measured using solid-phase fluorescence immunoassay, and urine creatinine was measured using the modified Jaffé kinetic method in the same laboratory[11] on frozen samples.

Definitions

Participants who responded "yes" to the question "Have you used or taken any vitamins, minerals, or other dietary supplements in the past month?" were asked to provide bottles for the individual supplements they took. Each provided supplement was classified as either potentially harmful in the setting of CKD or "other." A supplement was considered potentially harmful if it contained at least one of 37 distinct herbs identified from a literature review and expert opinion by the Council on Renal Nutrition for the National Kidney Foundation (NKF).[13] We reviewed supplement ingredients using the variable *dsdingr* (ingredient name) in the Dietary Supplement Database-File 4 to determine the presence of any of the 37 potentially toxic herbs. For ingredients noted as "proprietary blends," we located the actual product label to identify ingredients. In the event the product label could not be found, the variable *dsdbcnam* (blend component name, also in File 4) was queried. Participants were classified as taking any potentially harmful supplement, taking only "other" supplements, or taking no supplements.

We defined CKD status as no CKD; at risk only, by the presence of strong CKD risk factors (including diabetes, hypertension, or cardiovascular disease); stages 1/2 CKD, as albuminuria only (urine albumin-creatinine ratio $\geq$30 mg/g) with eGFR $\geq$60 mL/min/1.73 m^2; or stages 3/4 CKD, as eGFR of 15-59 mL/min/1.73 m^2, regardless of albuminuria. eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: $GFR = 141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] $\times$ 1.159 [if black], where SCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.[14]

We defined diabetes by participant self-report. Hypertension was defined by self-report or an average of second and third blood pressure readings $\geq$140 mm Hg systolic or $\geq$90 mm Hg diastolic. Cardiovascular disease included self-report of coronary artery disease, stroke, heart attack, congestive heart failure, or angina.

We categorized age into 3 groups (20-44, 45-64, and $\geq$65 years) and used NHANES categories of self-reported race/ethnicity as non-Hispanic white, non-Hispanic black, Mexican American, or other. Educational attainment was categorized as more than high school, high school or high school equivalent, and less than high school. We categorized income using the US Census Bureau's poverty index ratio (the ratio of family income to federal poverty level, where $\leq$1.00 is considered below the poverty level) into 3 groups (poverty index ratio $\leq$1.00, $>$1-$<$3, or $\geq$3). We included self-reported arthritis and cancer as comorbid conditions ascertained uniformly in our study population that may prompt individuals to take dietary supplements as a means of prevention or treatment.[15]

Tobacco use (no/past vs ongoing) was defined by significant lifetime use of cigarettes ($\geq$100), snuff ($\geq$20 times), and/or chewing tobacco ($\geq$20 times). Current alcohol use was categorized as none/moderate versus heavy ($>$7 drinks per week for women or $>$14 drinks per week for men). We defined health care utilization as the number of health care visits within the last 12 months as a continuous variable to examine the effect of encounters with health care providers on supplement use.

Statistical Analysis

We calculated the proportion of all reported supplements containing at least one NKF-identified herb and the proportion of potentially harmful supplements containing each specific NKF-identified herb. We used ordinal logistic regression to test whether supplement use varied by survey year. For US adults 20 years or older, we estimated the prevalent use of potentially harmful or only other supplements overall and by CKD status within groups defined by demographic characteristics, comorbid conditions, health-related behaviors, and health care visits. For the subpopulation of US adults who took any supplement, we used χ^2 analysis to test whether potentially harmful supplement use varied by CKD status within each of these groups. We estimated the frequency and duration of any potentially harmful supplement use and used χ^2 analysis to test whether these estimates were associated with CKD status. Finally, we used multivariable logistic regression to assess the presence, direction, strength, and independence of the association between taking a potentially harmful supplement and CKD status in those taking any supplement. We added covariates to the model sequentially to examine their incremental effects on the likelihood of taking a potentially harmful supplement. We performed sensitivity analyses with CKD defined by GFR estimated according to the isotope-dilution mass spectrometry−traceable

Table 1. Herbs From NKF List Found in Reported Dietary Supplements and Associated Adverse Renal Effects

Herb	Nephrotoxic	Aggravates CKD Risk Factor	Risky in CKD
Alfalfa	Triggers lupus	—	—
Aloe	Albuminuria, acute or progressive kidney injury	—	Hypovolemia
Bayberry	—	—	Hypovolemia
Broom	—	—	—
Buckthorn	Albuminuria	—	Hypovolemia
Capsicum	—	—	Hypovolemia
Cascara	Albuminuria	—	Hypovolemia
Dandelion	—	—	Hypovolemia
Ginger	—	—	Hypoglycemia
Ginseng	—	—	Hypoglycemia
Horsetail	—	—	Hypoglycemia
Licorice	—	High BP	—
Ma huang	—	Hyperglycemia, high BP, kidney stones	Hypovolemia
Nettle	Acute or progressive kidney injury	Hyperglycemia	—
Noni	—	—	Hyperkalemia
Pokeroot	—	—	Hypovolemia
Rhubarb	—	—	Hypovolemia
Senna	Acute or progressive kidney injury	—	Hypovolemia
Wormwood	Acute or progressive kidney injury, rhabdomyolysis	—	Hypovolemia
Yohimbe	Acute or progressive kidney injury, triggers lupus	—	—

Note: Hypovolemia due to diarrhea and/or vomiting.
Abbreviations: BP, blood pressure; CKD, chronic kidney disease; NKF, National Kidney Foundation.

4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[16] All analyses used recommended sampling weights[11] and were performed using the "svy" commands in Stata, version 12.0 (StataCorp LP) to account for the study design.

RESULTS

Participants in our study reported use of 5,280 distinct supplements, of which 14.3% (n = 757 unique supplements) were potentially harmful. Of the 37 NKF-identified herbs, 18 were found among supplement ingredients (Table S1, available as online supplementary material). Potential adverse renal effects of herbs found in reported dietary supplements are listed in Table 1.[17] Ginseng was the most commonly found NKF-identified herb, contained in an estimated 36.5% of potentially harmful dietary supplements, followed by ginger (23.6%), alfalfa (19.6%), capsicum (14.9%), licorice (14.8%), dandelion (10.3%), aloe (9.3%), ma huang (7.4%), nettle (7.4%), horsetail (6.0%), yohimbe (2.6%), rhubarb (2.3%), cascara (2.0%), noni (1.0%), senna (1.0%), and broom, wormwood, bayberry, and buckthorn (<1.0% each). The most commonly (>1%) reported potentially harmful supplements, including several multivitamin formulations, and their NKF-identified herbal ingredients are listed in Table 2.

Among US adults 20 years or older, supplement use did not vary across survey years ($P = 0.3$ by χ^2). An estimated 8.0% used a potentially harmful supplement(s) and an additional 44.5% used other supplement(s) (Table 3). These estimates were similar for participants who were excluded due to lack of kidney function data ($P = 0.8$ by χ^2). The overall prevalence of potentially harmful supplement use was lower with higher CKD status and older age, but that of other supplement use was higher with these characteristics. This pattern was similar by CKD status. Supplement use (potentially harmful and other) was most common among non-Hispanic whites, both overall and within each CKD status stratum. Overall, the prevalence of potentially harmful and other supplement use was higher among persons with higher income, educational attainment, and number of health care visits. A similar pattern was found in analyses within each CKD status stratum.

The vast majority of participants taking a potentially harmful supplement had done so nearly every day within the past month (Fig 1), and the frequency of use was not significantly different by CKD status (as defined by CKD-EPI equation, $P = 0.3$; or by MDRD Study equation, $P = 0.1$). Nearly one-third of

Table 2. Estimated Prevalence of Most Commonly Used Potentially Harmful Supplements

Supplement	Estimated Prevalence (%)	NKF-Identified Herb(s) in Supplement
Centrum Advanced Formula Carb Assist Complete Multivitamin/Multimineral From A to Zinc	3.4	Ginseng
GNC Men's Timed Release Senior Formula	1.7	Ginseng, nettle
Centrum Performance Complete Multivitamin Specially Formulated With Ginseng, Ginkgo, and Higher Levels Of 5 Essential B Vitamins	1.6	Ginseng
One Source Complete Women's With Ester-C Calcium 500 mg Cranberry EGCG (Green Tea Extract) Multivitamin Mineral & Herb	1.6	Ginseng
GNC Men's Ultra Saw Palmetto Formula	1.4	Ginseng
One Source Complete Women's Multivitamin/Multimineral/Herbs With EGCG Green Tea Extract 27 mg & Cranberry 50 mg	1.4	Ginseng
Member's Mark Advanced Multi Performance Multivitamin for Adults	1.3	Ginseng
Member's Mark Advanced Multi With Herbs	1.1	Ginseng
Metabolic Cleansing System 343 Advocare	1.1	Aloe
One Source Pure Performance The Advanced Formula Multivitamin Multimineral Herbs Formulated for Active Adults Complete	1.1	Ginseng

Note: n = 1,421, among US adults 20 years or older taking potentially harmful supplement, NHANES 1999-2008.

Abbreviations: EGCG, Epigallocatechin gallate; GNC, General Nutrition Centers; NHANES, National Health and Nutrition Examination Survey; NKF, National Kidney Foundation.

study participants taking potentially harmful supplements reported doing so for more than 3 years (Fig 2), which was increasingly common with greater CKD severity (as defined by CKD-EPI equation: 24.8% for no CKD, 32.9% for at risk, 40.1% for stages 1/2, and 50.5% for stages 3/4 [$P = 0.002$]; or by MDRD Study equation: 24.7% for no CKD, 32.9% for at risk, 40.8% for stages 1/2, and 45.1% for stages 3/4 [$P = 0.008$]).

Among supplement users (n = 10,224), the unadjusted model indicated that persons with or at risk of CKD had a lower likelihood of taking a potentially harmful supplement compared with those without CKD (Table 4). This finding was attenuated after adjustment for age. Additional adjustment for sex, race/ethnicity, poverty index ratio, educational attainment, comorbid conditions, tobacco and alcohol use, or number of health care visits did not significantly change these findings. Of note, the number of health care visits was not a significant independent predictor of taking a potentially harmful supplement. Results were similar when CKD status was defined by the MDRD Study equation (Tables S2 and S3).

DISCUSSION

Dietary supplements are widely used in the United States despite their potential for harmful effects.[18] Individuals with or at risk of CKD may be particularly vulnerable to harmful effects of supplement use through direct nephrotoxicity and other renal complications, as well as decreased clearance of substances, resulting in adverse product accumulation. To our knowledge, our study is the first to describe the use of dietary supplements potentially harmful in persons with and at risk of CKD in a nationally representative sample. Similar to findings in other studies,[5,6] we found that more than half of US adults (aged ≥20 years) reported taking any supplement within the 30 days prior to the survey. We show that approximately 1 in 12 US adults is taking at least one supplement that is potentially harmful in persons with kidney disease and that those with or at risk of CKD have a similar likelihood of taking such supplements compared with those without CKD, after accounting for important confounders. Certainly, our findings that potentially harmful supplements frequently are marketed under seemingly benign product names (such as multivitamins) and by trusted manufacturers, as well as that most individuals report taking them nearly every day and for prolonged periods, emphasize the scope of this issue.

The lack of variability by CKD status in taking potentially harmful supplements may be due in part to unawareness of CKD. An estimated 80%-90% of individuals with substantially decreased kidney function are unaware of their CKD.[19,20] Further, most individuals with CKD may be unaware they are at increased risk of harm given that consumers often assume "natural" products are safe and beneficial to health.[21] Unawareness regarding the potential harm of supplements also may be attributed to the lack of rigorous premarketing regulation and safety testing. With the passage of the Dietary Supplement Health and Education Act in 1994 (which classified supplements as a subcategory of food rather than a drug),[22] manufacturers were permitted to market supplement

Table 3. Point-Estimated Prevalence of Dietary Supplement Use Among US Adults 20 Years or Older by Characteristic and CKD Status

		Overall		No CKD (46.3% of total)		At Risk of CKD (39.0% of total)		CKD Stages 1/2 (8.0% of total)		CKD Stages 3/4 (6.6% of total)		
Characteristic	Column Percent	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	*P*[a]
All		8.0	44.5	8.5	40.4	8.0	46.9	6.1	44.1	6.2	58.9	<0.001
Age group												<0.001
20-44 y	49.0	7.6	35.1	8.0	34.6	7.1	36.4	5.4	32.4	9.2	47.7	
45-64 y	33.8	9.5	48.7	9.7	48.9	9.6	49.0	7.7	44.7	9.6	50.7	
≥65 y	17.2	6.0	62.9	6.3	66.0	6.6	64.5	5.1	58.3	5.3	61.3	
Sex												0.07
Male	50.2	7.7	38.7	7.4	35.4	8.4	41.0	6.0	39.0	6.7	50.1	
Female	49.8	8.3	50.3	9.6	45.7	7.7	53.0	6.2	48.4	5.9	64.8	
Race/ethnicity												0.002
Non-Hispanic white	72.0	8.7	49.6	9.3	45.4	8.9	51.6	6.1	51.3	6.9	62.1	
Non-Hispanic black	10.3	6.0	30.1	6.5	27.6	6.1	31.2	5.8	29.3	1.0	41.8	
Mexican American	7.6	5.4	25.2	5.4	22.6	5.8	27.2	4.6	30.2	2.5	43.0	
Other	10.1	6.4	37.2	6.9	32.4	5.4	43.5	7.7	34.4	4.9	44.4	
Income[b]												0.005
PIR ≤1	12.2	3.6	30.0	3.0	25.4	4.8	32.6	2.9	30.9	2.0	47.6	
PIR >1-<3	33.9	7.3	40.4	8.1	33.3	7.0	43.4	6.8	42.5	5.6	59.2	
PIR ≥3	53.9	9.3	50.3	9.8	47.6	9.3	52.0	6.9	50.8	8.0	61.4	
Education												<0.001
< High school	19.8	4.2	31.3	4.1	22.9	3.8	34.1	4.9	33.1	4.9	49.6	
High school	25.6	6.5	42.6	7.2	36.0	6.8	45.8	2.9	43.7	4.6	63.4	
> High school	54.6	10.0	50.2	10.2	47.3	10.2	52.2	8.6	50.5	8.5	63.2	
Diabetes												<0.001
No	92.5	8.1	44.2	8.5	40.4	8.2	46.5	6.5	44.9	6.5	60.2	
Yes	7.5	5.6	47.8	—	—	5.6	51.0	4.9	41.4	5.4	54.4	
Hypertension												<0.001
No	51.4	8.3	41.0	8.5	40.4	8.0	46.7	4.8	42.9	8.6	56.8	
Yes	48.6	7.6	48.1	—	—	10.4	46.9	6.8	44.7	5.8	59.4	
CV disease[c]												<0.001
No	91.3	8.1	43.6	8.5	40.4	8.2	46.3	6.4	42.0	6.9	60.0	
Yes	8.7	6.0	53.0	—	—	6.7	50.4	4.8	56.4	5.0	57.1	
Arthritis												<0.001
No	75.8	8.0	41.1	8.3	39.3	8.3	42.6	6.3	39.7	6.2	54.3	
Yes	24.2	7.7	54.9	9.6	47.1	7.4	57.5	5.8	53.0	6.3	62.9	
Cancer												<0.001
No	91.7	7.9	42.9	8.4	39.4	7.9	45.3	6.3	42.4	6.2	57.6	
Yes	8.3	8.6	61.2	10.4	60.1	9.2	61.6	5.0	58.5	6.3	63.4	
Significant tobacco use[d]												0.06
No/past	74.6	8.8	48.3	9.4	44.1	9.0	50.6	6.6	47.6	6.4	61.2	
Ongoing	25.4	5.7	33.2	6.1	31.1	5.2	35.4	4.9	34.7	4.6	39.3	
Heavy alcohol use[e]												0.008
No	71.7	8.2	45.3	8.8	41.0	8.3	48.6	5.4	44.3	6.7	60.3	
Yes	28.3	7.2	42.4	7.4	38.7	7.4	43.1	7.7	43.8	5.3	56.4	

(Continued)

Table 3 (Cont'd). Point-Estimated Prevalence of Dietary Supplement Use Among US Adults 20 Years or Older by Characteristic and CKD Status

	Overall			No CKD (46.3% of total)		At Risk of CKD (39.0% of total)		CKD Stages 1/2 (8.0% of total)		CKD Stages 3/4 (6.6% of total)		
Characteristic	Column Percent	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	Any Potentially Harmful Suppl	Other Suppl	*P*[a]
No. of health care visits in past 12 mo												0.001
0	16.5	6.7	30.0	6.0	30.8	8.1	28.1	5.1	27.3	10.1	44.0	
1-3	46.5	8.0	44.4	8.7	41.0	7.6	47.2	6.4	44.5	7.1	56.2	
≥4	36.9	8.5	51.1	10.0	47.0	8.5	52.2	6.2	48.5	5.6	61.1	

Note: "Column %" column shows the distribution of individuals within the listed categories. The remaining values are percentages of the given characteristic subgroup (ie, the row) who are using the indicated dietary supplement type overall and by CKD status as defined by CKD-EPI equation. N = 21,169, NHANES 1999-2008 (aged ≥20 years).

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; NHANES, National Health and Nutrition Examination Survey; PIR, poverty index ratio; suppl, supplement.

[a]The χ^2 test of association between potentially harmful supplement use and CKD status within characteristic, among those taking a dietary supplement.

[b]Defined using the US Census Bureau's PIR, the ratio of family income to federal poverty level, where ≤1.00 is considered below the poverty level.

[c]CV disease includes angina, heart attack, stroke, coronary artery disease, or congestive heart failure.

[d]Lifetime use of cigarettes (≥100), snuff (≥20 times), and/or chewing tobacco (≥20 times).

[e]More than 7 drinks per week for women or more than 14 drinks per week for men.

products directly to consumers without submitting proof of safety or efficacy to the US Food and Drug Administration. Consequently, marketing of these products often includes information that is inaccurate and possibly deceptive.[23-25] Furthermore, products often are not available in reliable or consistent potencies and dosages, making research on safety or efficacy extremely difficult.[26]

Although aristolochic acid nephropathy, a rapidly progressive interstitial fibrosis of the kidneys frequently leading to end-stage renal disease and urothelial carcinomas, is one of the most dramatic and highly cited examples of herb-induced nephrotoxicity,[27,28] ingestion of more common herbs contained in supplements may be an underappreciated source of nephrotoxicity or other adverse effects of particular concern in those at risk of or with advanced CKD. For example, dietary supplements containing herbs that increase blood pressure or worsen glycemic control may indirectly lead to or worsen existing CKD. Dietary supplements containing herbs that induce hypoglycemia or hyperkalemia may be of particular risk for those with advanced CKD. Older individuals and those with concomitant medication use may be particularly vulnerable.[3] Similarly, dietary supplements containing herbs that lead to diarrhea and vomiting may cause decreased kidney perfusion that results in acute kidney injury, an established CKD risk factor.[29,30]

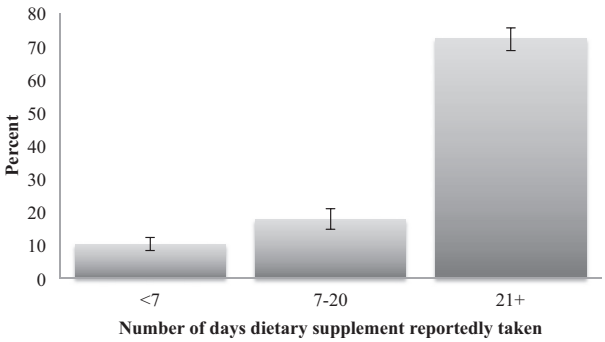

Figure 1. Frequency of supplement use in the last 30 days among US adults 20 years or older reporting potentially harmful supplement use, NHANES (National Health and Nutrition Examination Survey) 1999-2008.

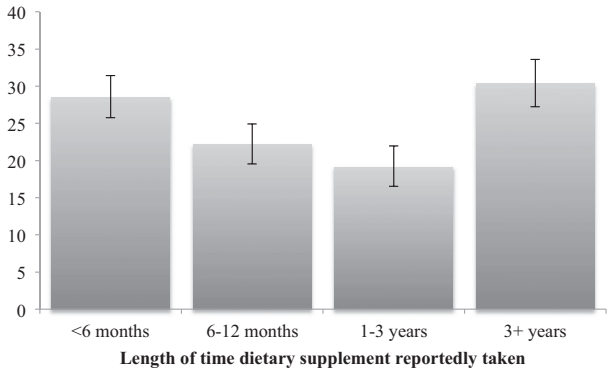

Figure 2. Duration of supplement use among US adults 20 years or older reporting potentially harmful supplement use, NHANES (National Health and Nutrition Examination Survey) 1999-2008.

Table 4. Odds Ratios for Taking Potentially Harmful Supplement (vs any other supplement) Among Dietary Supplement Users by CKD Status

	At Risk of CKD (14.7%)[a]		CKD Stages 1/2 (12.3%)[a]		CKD Stages 3/4 (9.6%)[a]	
Model	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Unadjusted	0.82 (0.70-0.95)	0.01	0.67 (0.51-0.87)	0.003	0.50 (0.39-0.66)	<0.001
+ Age group	0.92 (0.79-1.08)	0.3	0.81 (0.62-1.05)	0.1	0.84 (0.63-1.13)	0.3
+ Sex, race/ethnicity	0.92 (0.79-1.08)	0.3	0.81 (0.62-1.06)	0.1	0.85 (0.63-1.15)	0.3
+ Education, income	0.93 (0.79-1.09)	0.3	0.82 (0.63-1.08)	0.2	0.87 (0.64-1.18)	0.4
+ Arthritis, cancer, tobacco and alcohol use, health care visits	0.93 (0.79-1.09)	0.4	0.83 (0.64-1.08)	0.2	0.87 (0.63-1.18)	0.4

Note: n = 10,224; based on NHANES 1999-2008. CKD status defined by CKD Epidemiology Collaboration equation. Reference group is no CKD (which, among dietary supplement users, had a 17.4% point-estimated prevalence of potentially harmful supplement use).

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

[a]Percentage refers to the point-estimated prevalence of potentially harmful supplement use among dietary supplement users in this CKD category.

Because patients may be less likely to attribute harmful effects to dietary supplements,[21] there may be delays in diagnosing the cause of such complications.

Interestingly, we found that the prevalence of both potentially harmful and other supplement use was higher with higher number of health care visits. We expected that those with more health care visits would have a lower prevalence of potentially harmful supplement use because of more opportunities for health care providers to assess and advise against potentially harmful ingestions. This contradictory finding may be explained by people with chronic conditions having more frequent health care encounters and higher likelihood of complementary and alternative medicine use than those without a chronic condition,[15] but also may be a reflection of provider recommendations supporting the patient's use of generally accepted supplements (eg, vitamin D and calcium), but lack of awareness regarding the patient's use of potentially harmful supplements or CKD status. Provider unawareness may be due to a failure to ascertain whether the patient is taking other supplements coupled with provider unawareness of dietary supplement safety[31] and purposeful patient nondisclosure. This assertion is supported by our finding that the number of health care visits did not affect the likelihood of taking a potentially harmful supplement, but was an independent predictor for taking other dietary supplements (data not shown). In a national health survey of supplement users, only 33% of individuals and 51% of individuals with chronic conditions reported disclosing this use to their primary health care provider,[32] possibly due to skepticism of provider knowledge and attitude toward supplements.[21]

Prior research has shown that those with higher educational attainment and income are more likely to use supplements, possibly because these individuals are more knowledgeable regarding purported supplement indications and have greater disposable income for such purchases than less well-educated or affluent Americans.[33] In our study, the finding that prevalence of supplement use potentially harmful in kidney disease also was higher in adults with higher educational attainment and income may suggest a general lack of awareness of the risk these supplements may impose.

We recognize limitations of our study. First, because the NKF website is a prominent resource for public health education about kidney health, we chose to investigate only the herbs listed on the website because it may have served as a possible deterrent for potentially harmful supplement use for those with CKD. However, this list is unlikely to be exhaustive. For example, the list did not include acai berry, an herb touted for weight loss but that has cyclooxygenase 1 and 2 inhibitory action[34] like certain nonsteroidal anti-inflammatory drugs, which are associated with acute kidney injury in the general population[35] and with disease progression in those with CKD.[36] Further, the NHANES question to ascertain supplement use does not specifically include teas, which may be important but under-recognized sources of potentially harmful herbs. Therefore, our finding that ~14% of reported supplements are potentially harmful in the setting of CKD likely is conservative. A more comprehensive list of herbs may have resulted in even higher estimates. However, of herbs included on the NKF list and reported among our study population, broom was the only herb for which we found no associated literature for adverse renal effects. Therefore, our estimate of prevalence is unlikely to be an underestimation of prevalent use of potentially harmful supplements.

Similarly, we acknowledge that some herbs included in the NKF list may have potential benefits. Senna, for example, is widely prescribed for constipation and a recent uncontrolled pilot trial found that wormwood significantly decreased proteinuria in 10 patients with immunoglobulin A nephropathy.[37] However, given the lack of consistency between products,[26,38] the lack of rigorous safety or efficacy testing, and the tendency for patients to believe people are rarely or never harmed by supplements,[21] it is important to raise awareness of potential harm.

Moreover, we did not examine dosages of supplements taken and therefore cannot conclude that individuals taking potentially harmful supplements are taking enough to do significant harm. Given the wide variety of documented discrepancies in product label claims and actual content in addition to possible undisclosed contaminations,[38,39] true quantitation and comparison of dosages would be impossible without direct product analysis. Regardless, it is important to note that a substantial proportion of our study population reported taking supplements over many years, possibly placing themselves at risk of cumulative effects. Consistent with this possibility, we found that individuals with CKD were more likely to report long-term supplement use than those with preserved kidney function. Although we are unable to determine causality due to study design, this association highlights the need for further examination of the longitudinal relationship between supplement use and kidney function.

In conclusion, the use of dietary supplements potentially harmful in the setting of CKD is common regardless of CKD status, even after accounting for confounders. Further study of a more comprehensive list of potentially harmful herbs and repeated measures to determine the actual risk to kidney function or other organ systems resulting from supplement use is needed. Nevertheless, this study supports the recommendation that providers vigilantly ask patients about all ingestions and appropriately advise patients about potential risks within the context of their CKD status.

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SUPPLEMENTARY MATERIAL

Table S1: NKF list of herbs potentially harmful in the CKD setting.

Table S2: Estimated prevalence of dietary supplement use in US adults aged ≥20 years by characteristic and CKD status (by MDRD Study equation).

Table S3: Odds ratios for taking potentially harmful supplement (vs any other supplement) in dietary supplement users by CKD status (by MDRD Study equation).

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